Japanese Encephalitis in the USSR

N. I. GRAŠČENKOV

The author sketches the history of Japanese encephalitis in the USSR, where it has been thoroughly studied since it first occurred in 1938. After a brief outline of its epidemiology, he describes the pathogenesis, the signs and symptoms, and the pathophysiological mechanisms that make this form of encephalitis so dangerous. He also discusses the diagnosis and the methods of treatment and prevention practised in the USSR.

In the USSR, the viral etiology of tick-borne encephalitis was established in 1937. Mosquito-borne Japanese encephalitis occurred for the first time in the USSR in restricted seacoast areas near Khasan in early September 1938; it occurred in epidemic form. The disease usually began as an acute fever with very severe cerebral signs and symptoms, among them meningeal signs, deep unconsciousness, and mental disturbances.

Within an exceptionally short period, available data from previous studies on tick-borne encephalitis and on St. Louis encephalitis being taken into account, the real character of this acute infection was revealed. The virus was isolated from the brain post mortem and from the blood of patients, and several types of mosquito transmitting these forms of encephalitis were identified (Alperovič, 1946; Altšuller, 1947).

In 1939 the disease appeared again, with the same clinical picture. In subsequent years sporadic cases occurred in the same seacoast area. They became the subject of investigations in 1939-1944, carried out by expeditions of the USSR Institute of Experimental Medicine.

In 1945-1946, under my guidance, an expedition of the USSR Academy of Medical Sciences consisting of parasitologists, virologists, and neurologists studied the disease in North and South Manchuria and North Korea. The expedition was a success from the point of view of the results obtained. It was found that the mosquito-borne encephalitides studied since 1938 in restricted seacoast areas are identical with those studied in North and South Manchuria and North Korea. It was also found that these mosquito-borne encephalitides are identical with Japanese encephalitis, which occurred within the same period in some parts of Japan.

Special attention was paid to the characteristic features of the transmitters, to the discovery of natural reservoirs of the virus, to problems of epidemic spread among the local population, and to the clinical signs and symptoms, pathogenesis and pathological anatomy, and the problems of quick clinical diagnosis, effective therapy, and prevention.

Japanese encephalitis was again studied in subsequent years in the same regions. The studies mainly confirmed the previous findings and elucidated some not very significant points. Numerous strains of the virus of Japanese encephalitis isolated in the USSR proved to be identical in their biological and antigenic features.

EPIDEMIOLOGY

The epidemiological features of Japanese encephalitis and similar diseases are worth mentioning briefly in connection with the clinical characteristics of this type of encephalitis, particularly because of their value for the understanding of the pathogenesis and pathological anatomy of the process, as well as of the clinical picture.

Epidemiologically, Japanese encephalitis in the USSR seacoast area was characterized by the same main features, but some peculiarities were noted. For instance, cases were observed only among the rural population; there were none in towns.

The epidemiological features could be explained by postulating mosquitos as transmitters. This was
confirmed by infecting albino mice and monkeys through the bites of mosquitos after they had sucked the blood of infected animals, as well as by detecting mosquito carriers in foci of encephalitis during the epidemic period. Among mosquito carriers the main species are: *Culex pipiens fatigans*, *Culex tritaeniornynchus*, *Culex bitaeniornynchus*, *Aedes japonicus*, and *Aedes togoi*. The role of mosquitos in disseminating encephalitis was also confirmed while the epidemiology of this disease was being studied in seacoast areas in the USSR.

During the epidemic period a wide dissemination of virus takes place among people and animals. Many domestic animals (horses, cows, pigs, goats) and wild animals (rats, hamsters), birds (sparrows, pheasants), and people are carriers of the virus. In the overwhelming majority the infection does not produce disease, but only results in a short viraemia with subsequent development of immunity. This is confirmed by the regular discovery of antibodies in the blood of people and domestic animals in regions of epidemic distribution of encephalitis. Natural immunization is the most important factor restricting the distribution of the disease. In epidemic regions the incidence decreases with the increase in the immune group.

There is a considerable danger of people newly arrived in epidemic areas contracting encephalitis. For example, cases occurred among American troops during the epidemic of 1945-1948, as well as among Soviet troops in the Kwantung peninsula in 1945-1946 (Graščenkov, 1949; Radkevič, 1947).

Mosquitos are infected while feeding on animals, birds, and man during the period of viraemia, and in their turn disseminate the virus. The main sources of the infection of mosquitos are undoubtedly domestic animals and wild birds. The question of viral reservoirs during inter-epidemic periods remains unsolved. Burnet (1952) has propounded the hypothesis that ectoparasites of domestic animals and wild birds maintain the circulation of the virus during the winter. He believes that birds are infected by mosquitos in the tropical zones and that during seasonal migration to northern latitudes they infect other mosquitos, thus causing new foci of infection. This hypothesis has constantly been buttressed by new facts.

It must not be thought, however, that the study of the distribution of Japanese encephalitis has been completed. Some solitary cases of Japanese encephalitis and some mild forms of infection may be peculiar to old endemic foci.

**PATHOGENESIS AND PATHOLOGICAL ANATOMY**

In our opinion, for the understanding of the clinical features of this form of encephalitis, knowledge of the pathogenesis and pathological anatomy of the process is of the greatest importance. The problems have been thoroughly investigated by our collaborators and ourselves since 1938 (Graščenkov, 1947a; 1947b). Careful observations have been made of the signs and symptoms of Japanese encephalitis, various clinical and physiological techniques have been applied, and histopathological analysis has been made of the central nervous system of experimental animals and of people who have died from the disease.

The characteristic features of the pathogenesis of Japanese encephalitis are to a considerable degree determined by the way in which the virus penetrates into and circulates in the human body. A massive attack by infected mosquitos on man and, therefore, the inoculation of virus into many people within a relatively short period of time give rise to considerable epidemic outbreaks.

A number of factors, such as overheating, malnutrition, chronic parasitic and bacterial infections, and inadequate living and working conditions, lower the defences of the body and contribute to the infection by the neurotropic virus. They also favour an acute onset of the disease—or even without—a short prodromal period. The virus, on inoculation by mosquitos, is partially destroyed at the site of penetration; what survives is disseminated by the blood stream throughout the body. The virus acts first on the endothelial walls of capillaries and precapillaries of parenchymatous organs and the brain. It also multiplies in the blood stream, and, breaching the blood-brain barrier, quickly reaches various cerebral structures. Having penetrated the cerebral parenchyma, especially neurons with specific biochemical characteristics, it begins, because of its neurotropic properties, to multiply rapidly; and then, because of its high cerebral concentration, it again enters the blood stream and is disseminated through the whole body.

The critical point in the incubation period may be when a large amount of virus has built up and penetrated into the cerebral parenchyma. This is quite in keeping with data regarding the amount of virus in the blood and viscera at the end of the incubation period and during the first days of the onset of clinical symptoms. By this time the viral concentration is such that the toxic inflammatory
processes involve not only the central nervous system but the viscera as well, because simultaneously with the cerebral lesion there is a severe lesion of parenchymatous organs, including the lungs, liver, and myocardium.

Experiments carried out by virologists in the USSR with the purpose of elucidating the mechanism of the dissemination of virus from the periphery to the centre confirm that it is by the blood stream. This is also indicated by the extent of the diffusion and by the predominance of the toxic inflammatory process in the hypothalamus and midbrain, this being directly connected with the characteristic features of the blood supply of these regions.

The penetration of virus through the endothelial walls of the capillaries and precapillaries results in an appreciable increase in the permeability of the cerebral vessels and those of other parenchymatous organs to plasma and blood elements.

Overheating of the body plays an essential role in altering the permeability of the blood-brain barrier, as has been shown in a series of experimental studies carried out by Stern and her collaborators (1960).

Having penetrated through the endothelial walls of capillaries and precapillaries and crossed the blood-brain barrier, the virus attacks the next mesenchymal defence of the brain, which is the complex of macroglial and microglial cells. These cells are different in structure and purpose. The main glial elements are astrocytes, star-shaped cells with numerous processes, some of which are always to be found in relation to the walls of the small cerebral vessels. There exists, however, another type of astrocyte, the so-called protoplasmic astrocyte, which does not have numerous processes and is situated both near the walls of vessels and between neurons and their fibres, forming something like a support for the latter. Under certain conditions these cells are capable of phagocytosis. Between neurons and their fibres and in close relation to the smallest cerebral vessels everywhere there are smaller glial cells, called oligodendroglial cells or oligodendroglia. In the brain there are also numerous macroglial or Hortega cells, which by many authors are looked upon as histocytes that have migrated into the nervous tissue.

All the above-mentioned glial cells make up the mesenchymal barrier, the function of which is to combat viruses and toxins penetrating the blood-brain barrier and reaching the cerebral parenchyma. These glial cells, though in different ways, defend in the most active way against infection, including Japanese encephalitis virus. They form the next line of defence following the destruction of capillary endothelial integrity, the attack by the virus being met by the astrocytes with processes.

The struggle is manifested by different degrees of destruction of glial cells, such as the breaking and segmentation of astrocytic processes, swelling, and the break-down and loss of cell bodies. Protoplasmic astrocytes play the role of "orderlies", clearing the field of battle of the dead astrocytes with processes and oligodendroglial elements. Macroglial cells or Hortega cells quickly replace the glial elements and neural cells that have been destroyed. Hortega cells multiply and form glial scars, which separate intact from destroyed nervous tissue by a mesenchymal barrier. While the first phase of the viral attack involves destruction of endothelial integrity and reduction of its protective properties—this being connected with the processes of exudation and transudation—the second phase involves the destruction to a varying extent of single glial elements and subsequent proliferation and partial restoration.

After penetrating and destroying the second, mesenchymal, barrier, the virus of Japanese encephalitis reaches the nerve cells and their fibres. Then the last stage ensues, in which nerve cells are destroyed; various phases of destruction being observable from cell oedema and swelling to breaking and segmentation of the neural processes, and, finally, break-down of the cell itself followed by phagocytosis and replacement by microglial elements.

Apart from the states produced by considerable exudation and transudation, various degrees of cerebral tissue oedema occur. The oedema is further increased by exudation owing to the permeability of the endothelial walls and the flow of fluid from the main tissues to parenchymatous organs, particularly the brain. All these processes involve the hypothalamus, where the centres for water and protein regulation are situated, and the result is aggravation of the oedema of the brain and of other parenchymatous organs.

The histopathological picture of Japanese encephalitis can be presented in general lines as consisting of:

(a) lesions of the capillary and pericapillary endothelium of the brain and parenchymatous organs, with more or less extensive haemorrhage;

(b) oedema of the brain and other parenchymatous organs;
In the brain, capillaries and precapillaries; and exudation and proliferation in the cerebral parenchyma accompanied by cerebral tissue oedema.

As far as the localization of pathological changes in the brain is concerned, in spite of the dissemination and generalization of the infection it should be stressed that the degree of severity of the main lesions differs in different regions of the brain. Undoubtedly this is related to the difference in the blood supply to the various cerebral tissues. In the same volume of cerebral tissue in different areas there are different numbers of very small blood vessels. For instance, there are 100 times as many blood vessels in the hypothalamus as in some regions of brain. It was shown long ago that the vulnerability of the subcortical formations is dependent upon their particular blood supply. That is why different degrees of severity are observed in Japanese encephalitis.

If we try to determine the vulnerability of the various parts of the central nervous system, we shall see that the intensity of the process is undoubtedly less in the cerebral cortex than in the hypothalamus and midbrain. Moreover, in the cerebral cortex itself the intensity of the process varies; for example, it is greater in the frontal lobes than in the rest of the cortex, though, because of the considerable oedema, all regions of the cerebral cortex are involved in this disease. The process is rather more severe in the subcortical formations. The intensity increases in the thalamus and especially in the hypothalamus, and is particularly marked at the level of the red nucleus and substantia nigra. As well as in the brain, different degrees of intensity are observed in the viscera, especially in the parenchymatous organs (lungs, liver, kidneys). Here widespread congestion and in some cases haemorrhage and oedema may be seen. These conditions may also occur in the adrenal glands, the gastro-intestinal mucosa, and the myocardium.

Visceral lesions are caused both by direct injury to the capillaries and precapillaries and by the widespread damage to the regulatory centres in the hypothalamus.

This dual causation of oedema in the brain and parenchymatous organs needs to be stressed. Oedema occurs because of the endothelial lesions of capillaries and precapillaries and the transudation of blood plasma into the cerebral parenchyma, but also because of lesions of the water and protein regulatory centres in the hypothalamus. As a result, the distribution of fluids in the tissues of the body becomes irregular; the circulation is one-way only, from the tissues to the parenchymatous organs.

Macroscopically, sections always show hyperaemia of the meninges and brain substance. In particular, hyperaemia of the subcortical formations is clearly seen. In the putamen there are many disseminated brown points, obviously small necrotic foci. In the frontal lobe reddish staining of the grey matter may be observed, related to the capillary hyperaemia. The same staining may be observed in the temporal lobe, in the region of Sylvius' fissure.

Microscopically, the meninges of the brain and spinal cord are always slightly oedematous and very congested. The blood vessels of the brain, medulla oblongata, and spinal cord are dilated and congested, and stasis is present; in some places diapedetic haemorrhages may be noticed. The vessel walls are oedematous and their endothelium swollen but rupture of the vessels is not observed. In two cases, meningeal haemorrhages were seen in the occipital region, with rupture of the marginal sinus and escape of blood into the brain substance.

The meninges are infiltrated with macrophages, lymphocytes, and some polymorphonuclear neutrophils. In some places the infiltrating cells penetrate by the blood vessels into the brain substance, breaking the integrity of the gliomesodermal barrier. In the cortex there is considerable oedema; hyperaemia of all the blood vessels down to the smallest branches may be observed. The accumulation of liquid exudate and in some places of pink masses around the blood vessels points to a disturbance of permeability. Stasis is common and diapedetic haemorrhages frequent. Sometimes red cells in blood plasma are mixed up with the perivascular infiltrations. There is an extraordinarily great proliferation of the precapillary vascular endothelium and here and there desquamation is visible with obstruction of the lumen.

The vascular walls are infiltrated with lymphocytes and polyblasts, but to a moderate degree. In some cases the infiltrating cells occupy all the layers of the vascular wall; in most, however, the inflammatory
infiltrate is restricted to the adventitia, but at the same time severe disturbances of barrier function often take place when elements of the infiltrate breach the barrier and penetrate into the surrounding cerebral tissue. This occurs in the cortex, and especially in the subcortical formations, the hypothalamus, and the substantia nigra, as well as, to a more limited extent, in the pons varolii and medulla oblongata.

In the marginal layer intense microglial proliferation is observed. Among the Hortega cells rod forms predominate. The nuclei of these cells are partially pyknotic and wrinkled and the processes swollen.

CLINICAL SIGNS AND SYMPTOMS

As has been shown above, Japanese encephalitis is an extremely serious condition, with marked general signs and symptoms of infection, meningeal and general cerebral involvement, and, in the background, focal cerebral lesions that involve principally structures at the hypothalamo-subcortical and reticular formation level.

According to epidemiological data, the duration of the incubation period is most probably 4-14 days. In most cases the onset of the disease is sudden, without a distinct prodromal period, but sometimes a prodromal period is observed. Such a period is very short, not longer than two days, and is characterized by increasing headache, generalized aching over the whole body, chilliness, and lack of appetite. Acutely developing forms do not produce such a prodromal period.

In some cases the full picture of a severe infectious illness with meningo-encephalitic signs develops within the first 24 hours. The patient’s appearance is notable because of the marked facial and conjunctival hyperaemia as well as the characteristic posture in bed. He lies on his back or on his side, his head slightly thrown back, his arms bent at the elbows and wrists, his shoulders pressed to his chest, his legs a little drawn up or stretched out. Consciousness is disturbed, the disturbance taking the form of stupor and deafness. In some cases there are delirium with agitation and incoherent speech. Within 2-3 days the disturbance of consciousness and other encephalitic signs increase. Delirium and stupor are replaced by coma; there may be paresis of the limbs, epileptiform seizures, hyperkinesis, and (in a severe case) bulbar signs.

In two severe epidemic outbreaks we and our collaborators (Graščenkov, 1949; Sergeeva & Drigo, 1947) found the course of Japanese encephalitis to be fairly constant, with characteristic signs and symptoms. We attempted to correlate our findings with the different phases of the infection in the central nervous system, and devised accordingly a system of hourly treatment aimed at counteracting the main pathogenic effects. On the basis of careful investigation, we distinguish the following four stages of the disease:

(1) The primary or initial stage occurs in the first 2-3 days of the disease. It is characterized by a very high temperature, signs of general infection and toxicity, and relatively few indications of focal neurological lesions.

As a rule, during the initial stage there may be present occipital muscular tension and confusion of varying degree (or complete loss of consciousness), a rapid pulse, altered muscle tone—in the direction of greater tension, especially of the extensors—a functional change in the oculomotor muscles, and absent pupillary reflex.

We attach great importance to the distinguishing of this stage in the course of the disease. In our view, during this initial period there is a massive dissemination of virus through the disturbed capillary and precapillary walls into the cerebral parenchyma, resulting in oedema of the cerebral tissue.

This is the first phase in the clash of the virus with the mesenchymal defences of the body. The cellular elements of the nervous system have not yet been destroyed by the virus.

(2) The second stage that we distinguish is the acute stage, which corresponds to the 3rd and 4th days of the disease (or to the 5th and 6th when there is a prodromal period). This is a period of stable or slightly fluctuating high temperature. Signs of local cerebral lesions are frequent. The general cerebral signs characteristic of the initial stage are aggravated and remain constant: loss of consciousness deepens; muscle tone and occipital muscle tension increase; the supraspinal and tendon reflexes grow weaker or even disappear; marked sweating occurs; distinct hyperaemia of the face, sclera, and upper thoracic region is seen; the disturbance of the oculomotor muscles intensifies; the light reflex changes; more distinct cortical, subcortical, and brain stem signs appear. During this stage decerebrate rigidity is marked, especially in serious cases. The acute stage is decisive for the fate of the patient; if we succeed in keeping him alive, we can hope for his complete recovery.
From the pathogenetic point of view, we consider the acute stage as a phase of diffuse penetration of the virus into the cerebral parenchyma. Multiplication of the virus produces a disturbance of the mesenchymal barrier, which inevitably results in increased toxicity and more oedema of the cerebral parenchyma. In the acute period numerous minute haemorrhages occur. All this results in disturbed function of the cerebral cortex and the subcortical and sometimes the brain stem structures. If during the acute period cardiac action and respiration are not maintained systematically, and if the threatening cerebral and pulmonary oedema is not dealt with, there may be cessation of the functions most important for life (cardiac action and respiration).

There is no doubt that it is at this period that the virus acts upon the neural elements themselves—the neurons and the groups of nuclei at the bulbar and hypothalamo-subcortical levels.

(3) The third stage of the disease is the subacute stage of decreasing subfebrile temperature. During this period some cerebral signs develop and others become stabilized. Consciousness becomes lighter but is not fully restored. The pulse gradually slows down, though in some cases relative tachycardia is observed for a long period. Muscle tone decreases. The subspinal and tendon reflexes become stronger, and may even become marked; they may be elicited on one side only, indicating hemiparesis, and this will correspond to decreased muscular power on that side and be accompanied by distinct patho-
logical signs such as Babinski's and Oppenheim's. Pathological signs may of course be seen during the initial stage, and disappear or remain during the acute stage, to appear again during the subacute stage. They also depend on the degree of muscle tone; where there is marked hyperextension, the weakness of the pyramidal system is not always manifested in the form of extensor-flexor reflexes.

In the subacute stage disturbance of co-ordination may as a rule be demonstrated. Diadochokinésia, the finger-nose and knee-heel tests, as well as Romberg's sign, point to this and indicate weakness of bulbar-cerebellar and reticular structures.

The subacute follows the initial and acute stages and covers the 7th-10th days. During the subacute stage early complications of Japanese encephalitis may occur in the form of pneumonia, pyelocystitis, thrombophlebitis, and so on.

(4) The fourth stage of the disease is the residual or convalescent stage. Usually during this period the temperature is normal or slightly raised; there are residual signs of cerebral organic lesions (hemiparesis, disturbance of co-ordination, general muscular weakness, cardiac signs, disturbances of memory, and other signs of cerebral asthenia). In some cases during the convalescent period there are mental disturbances of a schizoid type (hebephrenia or manic-depressive psychosis, sometimes with delusions of grandeur, etc.).

In this period late complications can be observed: pneumonia, pyelocystitis, or bedsores. Disturbance of carbohydrate metabolism of a hypoglycaemic type and autonomic disorders usually occur at this stage too. The convalescent stage lasts 4-7 weeks.

In Japanese encephalitis the temperature curve is of great importance in the various stages. In spite of the diversity of curves, especially in connection with complications at the subacute and residual stages, all the variants of the temperature curve can be divided into the following four types:

(1) A high temperature suddenly rising to 40°C or a little higher and persisting for 5-6 days. This temperature curve is characteristic of the most severe and acute forms of Japanese encephalitis, the outcome of which is as a rule fatal.

(2) A temperature rising within 48-72 hours from subfebrile in the prodromal period to 40°C or a little higher. It varies by about only 1° during a period of 5-6 days and is followed by a gradual fall. This temperature curve is characteristic of severe but not fulminant forms of Japanese encephalitis; some cases are fatal, most often within 7-12 days of the onset of the disease.

(3) A temperature rising from subfebrile in the prodromal period to 40°C and persisting at this level for 48-72 hours. Then there is a gradual drop, though in some cases it is abrupt. With the abrupt drop of temperature the outcome may be fatal because of cardiac weakness; however, half the patients recover. This type of temperature curve is characteristic of forms of the disease of moderate severity with rather a rapid course.

(4) A temperature for the first 5-6 days approximately the same as that of the third type, but with subsequent rises, which may be repeated and lasting owing to complications in the subacute stage (bronchopneumonia, pyelocystitis, sluggishly developing bedsores, and so on). In some cases a fatal outcome is possible, especially if there is an increase in the complications.
PATHOPHYSIOLOGICAL MECHANISMS OF JAPANESE ENCEPHALITIS

In this section we deal with the characteristics, pathophysiological mechanisms, localization in the central nervous system and dynamics of the four main stages of the disease.

As has been mentioned above, in the prodromal period some indications of irritation of the meninges are headache, tension of the occipital muscles, and occasionally Kernig’s and Brudzinski’s signs.

Without denying the meningeal nature in general of the above-mentioned signs, one should emphasize, however, some discrepancy between the degree of occipital muscle tension (severe opisthotonos) and the extent to which Kernig’s and Brudzinsky’s signs are manifested, as well as between these signs and the cerebro-spinal fluid test. Thus these signs, especially occipital muscle tension, are not meningeal in the full sense of the word. Occipital muscle tension is a typical cervical tonic reflex phenomenon studied by Magnus and Klein and occurring in various states of decerebration, e.g., on separation of the cerebral hemispheres and subcortical formations from the medulla oblongata at the level of the midbrain. Because of the early occurrence of cerebral oedema in the subpial space signs of meningism are produced. But occipital muscle tension is mainly connected with the decerebrate mechanism.

As early as the prodromal period there are complaints of aching over the whole body and severe muscular pains. These pains become marked hyperaesthesia in the acute, subacute, and residual stages, which according to histopathological knowledge indicates a lesion of the thalamus, one of the first structures involved in the process.

Soon, however, other signs point to a lesion of the cerebral cortex or reticular formation (various degrees of disturbance of consciousness, somnambulism, labile aphasic disorders); in some rare cases in the initial or acute period clonic spasms may occur. In disturbance of consciousness there may be sphincteric paresis. Hemiplegia may be observed occasionally in the acute stage. In spite of greatly increased muscle tone this hemiplegia then turns into hemiparesis in the subacute and residual stages. The signs indicating lesions of the frontal lobes are very distinct. A severe disturbance of complex motor co-ordination occurs, and in addition there is prolonged apraxia pointing to a lesion of the lower parietal region of the cerebral cortex. The characteristic feature of these conditions is inability to repeat the most simple movements. They are well demonstrated in the subacute and residual stages, after consciousness is recovered.

The signs of lesions of the cerebral optical cortex (flashing points of light, etc.) are also very clear-cut.

In the acute stage, in spite of very severe disturbance of consciousness, the grasp reflex, which is pathognomonic of frontal lobe lesions, can be very distinctly seen in some cases.

In the subacute and residual stages, the signs of lesions of the optical cortical system are manifested by different degrees of narrowing of the field of vision when subjected to white and especially coloured stimuli.

The temporal region of the cerebral cortex does not remain unaffected either, signs and symptoms of lesions being observable in the subacute and residual stages. These are a sensation of dizziness (although the vestibular apparatus is quite normal) and buzzing in the ears. This indicates involvement of both the cochlear branch of the eighth cranial nerve and the higher level of hearing function in the temporal lobes.

Both in the acute and in subsequent stages (especially in the subacute) distinct signs of functional disturbance of the subcortical regions are observable, particularly of the subcortical structures: the face is waxen and mask-like, and different forms of hyperkinesia of the pill-rolling type or choreoathetoid and choreiform movements become manifest; in some cases there are forced laughter and tonic spasms without a clonic component. In spite of these distinctive signs of subcortical lesions Japanese encephalitis does not turn into post-encephalitic parkinsonism, perhaps owing to the severity of the lesion affecting the substantia nigra; in von Economo’s encephalitis the substantia nigra is affected to a lesser degree and the subcortical formations to a greater.

There are very many signs of lesions of the hypothalamus. The most obvious is disturbance of thermoregulation. A high temperature in patients with Japanese encephalitis and exceptional temperature fluctuations point to a lesion of the thermoregulatory centre. This lesion is obviously not connected with respiratory distress. It may cause facial hyperaemia and a varying amount of sweating.

In the acute, and especially in the subacute, stage, signs of metabolic disturbances of different types (protein, fluid, and carbohydrate) are very marked. They are manifested by extreme thinness, exhaustion, dryness of the skin, dehydration, and disturbed circulation of body fluids, which move in one
direction only, from the tissues to the parenchymatous organs. The tongue is white and furred, and there is hypoglycaemia, greatly decreased blood sugar being found in the residual stage in more than half of the patients. In 50% of patients examined it was 45-70 mgm%.

Different degrees of dystrophy may occur. They may be seen not only in the form of early, sluggishly developing bedsores, but also in the form of ulceration of the gastro-intestinal mucosa. Thus clinical experience confirms the pathophysiological experiment of Speranskij (1937), who found that stimulation of the hypothalamic region causes the animal to develop dystrophy of varying degree.

Functional disorders of the hypothalamic region in Japanese encephalitis also account for an unusual cardiovascular lability. As a rule, even in the initial period the pulse quickens to 120-140 per minute. The volume is full, and in sphygmography the pulse wave is much increased. This type of wave persists to a considerable extent in the residual stage, dropping in the final stages before death. The blood pressure in the acute and subacute stages is high, and in the residual stage may be normal; or, alternatively, both systolic and diastolic pressures may even be reduced. The transition from tachycardia to bradycardia is observed very rarely.

Aschner's sign is very marked in the subacute and residual stages.

The peripheral capillaries decrease in calibre, becoming very constricted. Electrocardiography in the subacute and residual stages in all cases shows functional disturbance of the heart typical of postinfectious myocarditis (4% of cases), or of minute haemorrhages (e.g., very small infarctions) (20%), or of great myocardial lability (30%), or, finally, of conduction disturbances (50%). However, it should be noted that these conditions are reversible.

Somnolence and pathological sleep in the acute and subacute stages can be explained not only by the variable loss of consciousness but, especially after the recovery of consciousness, by lesions in the reticular formation affecting the regulation of sleep and wakefulness. The activity of the cerebral cortex is also concerned.

Thus no hypothalamic function is left undisturbed in Japanese encephalitis. Happily the effects are reversible if the patient is actively treated during the disease.

The most obvious sign of midbrain lesions is great muscular rigidity and very marked cervical tonic reflexes or opisthotonos. This sign persists longest. The presence of decerebrate rigidity is shown by marked extensor reflexes, flexed arms and extended legs.

Pyramidal disturbance of oculomotor function is clearly marked. It is manifested by unilateral or bilateral ptosis, in most cases with anisocoria and in some with enophthalmos. Other signs are deficient convergence and accommodation, functional deficiency of the nerve, and oculomotor paresis.

In severe cases during the acute stage signs of medulla oblongata lesions are seen, some of which may persist into the residual stage. There are pareses, and, in some cases only, facial palsy of central origin. Usually these pareses are unilateral, but they may sometimes be bilateral. There is a functional lesion of the cochlear branch of the acoustic nerve, manifested by impairment of hearing and buzzing in the ears. Functional disturbance of the ninth cranial nerve is seen, in the form of prolonged disorganization of taste. Motor disturbances of the tenth cranial nerve are shown by unilateral or bilateral paralysis of the velum palatinum. Finally, functional disturbance of the twelfth cranial nerve is manifested by reduced ability to protrude the tongue, its deviation to the right or left from the midline, and fibrillatory twitching. In most patients these disturbances are pyramidal in origin, and only in some are there nuclear lesions of the cells of the medulla oblongata.

Signs of spinal-cord lesions are observable, especially in severe cases. These lesions are mainly in the white matter of the spinal cord. They are manifested by high supraspinal and tendon reflexes in the subacute and residual stages, when muscular hypertonus decreases; by the generalization of the reflexes—eliciting a knee jerk on the right results in a generalized response of all the muscles of the left limb and even of the trunk--; and by spinal automatism in the form of distinct protective reflexes to painful or cold stimuli or on compression of the foot. This spinal automatism is so clearly seen that it might form a demonstration of the classical physiological experiment with a spinal preparation. It may be considered as a residue of decerebration. Among other spinal cord lesions we may mention sphincter disorders and rapidly developing bedsores, though in these lesions there is a dual mechanism, spinal and hypothalamic for bedsores and spinal and cortical for sphincter disorders.

The numerous neurological symptoms indicate the great diffusion of the disease process and its acute
course. The reversibility of most effects indicates that they are caused by circulatory disturbances, particularly oedema of various parts of the brain. In addition, there is disturbance of blood and spinal fluid dynamics.

The blood-brain barrier in Japanese encephalitis was studied most comprehensively by our collaborator Kartaševo (Glazunov, Kartaševo & Hvan, 1948). In the subacute, but mainly in the residual, stage permeability of the blood-brain barrier is disturbed, in respect mostly of sugar but also to some extent of chlorides. The permeability quotient of sugar in 75% of cases was 0.6-0.34; that of chlorides was not altered so drastically, and changed in only 46% of patients. Alterations often occurred together in the permeability coefficients of sugar and chlorides.

It is interesting that in the acute stage the coefficient of permeability of sugar and chlorides changed in only one out of nine patients examined, but this is not a sufficient reason for believing that there is no change in blood-brain barrier permeability at this stage. On the contrary, tests of the spinal fluid in the acute stage clearly showed positive for globulin in all cases, while the protein was below normal and the cell count low. This indicates that the blood-brain barrier is permeable to the globulin fraction, which under normal conditions it is not. Finally, the whole development of the attack by the virus on the central nervous system, with the primary lesion in the vascular endothelium, undoubtedly points to a breach of the blood-brain barrier at the earliest stage of the disease.

The morphological changes in the composition of the blood are similar to those described by Japanese authors. They consist in most cases of a considerable leukocytosis (in the acute stage 9000-15 000 per mm³), and only in some cases is there leukopenia, which is evidently connected with complicating factors. Among the leukocytes there is a considerable increase in the number of neutrophils (up to 74-85%); there is no clear shift to the left, to rod forms. The lymphocyte count is correspondingly decreased, eosinophilia is observed in nearly 100% of cases, and monocytes occur rarely at the culmination of the disease. The leukocyte count and distribution usually return to normal during the fifth and sixth weeks. In the first days of the disease there is moderate leukocytosis, the haemoglobin is about normal, and the colour index and sedimentation rate are high. In the residual stage, when the blood picture returns to normal, exceptional responsiveness of blood to the slightest pathological change is observable. Thus a complication not yet clinically obvious may be revealed by leukocytosis (sometimes up to 18 000-25 000 per mm³), and by increasing numbers of neutrophils, in particular rod forms. With such a blood picture the physician should look for complications; that is why blood examinations should be compulsory for patients with Japanese encephalitis.

Changes are also found in the urine: increase in the specific gravity, albumin—varying in amount from traces to large quantities—and, with complications affecting the urinary tract, increased numbers of leukocytes and erythrocytes in the urinary sediment. Systematic urine testing at different stages of the disease is therefore also the responsibility of the attending physician.

The cerebro-spinal fluid in the acute period is always clear and colourless. As a rule, the albumin is below normal or does not exceed it (0.1-0.25%). The number of cells is inconsiderable; in 50% of cases it does not exceed the normal, in the other 50% it ranges from 20 to 40 cells per mm³, and only in rare cases does it rise to 200-400. The globulin test, irrespective of the amount of albumin, is always positive, and in most cases strongly positive. The explanation of this has been given above in connection with the permeability of the blood-brain barrier.

The spinal fluid in the subacute and residual stages presents quite a different picture. There was increased albumin in 97% of all cases, and in 78% it ranged from 0.51% to 2%. All cases of albuminuria are accompanied by a high positive result in the globulin test; in the residual stage there is a considerable increase of formed elements in the cerebro-spinal fluid (from 50 to 600). Such shifts in the fluid in the acute and residual stages are related to the dilution of albumin in the acute stage owing to great cerebral oedema, and to the fact that the absence of sufficiently manifested repair processes does not influence cell formation. In the residual stage, in which the repair processes in the brain are obvious, a considerable increase in the number of cells takes place, and increase in the albumin is related mainly to increased permeability of the blood-brain barrier, and, to a smaller degree, to the breakdown of cerebral albumins caused by destructive processes.

The changing picture of the fundus in the acute and residual stages is most interesting. In the acute stage, as a rule, hyperaemia of the optic disk and (in a certain percentage of cases) haemorrhages are
observed; in a smaller percentage of cases oedema occurs. In the subacute and residual stages residual haemorrhages in the fundus, residual signs of oedema, congestion, and neuritis, which is sometimes progressive and most severe, and even atrophy of the optic nerve are observed. Light, and especially colour, sensation is severely disturbed. Narrowing of the field of vision, especially in relation to colour sensation, and the presence of different photopsies and scotomas are noted.

All these processes in the fundus and retina are related to lesions both of the peripheral optic apparatus and the cortical optic centres, and are produced by hyperaemia, oedema, and spot haemorrhages.

The mortality in Japanese encephalitis is unusually high (from 40% to 70%). The overwhelming majority (70%) of deaths occur within the first 7 days. The rest occur from the 8th to the 15th days but in some cases later—up to the 30th day. Death is connected with the complications that occur—bedsores, pneumonia, sepsis, even metastatic abscesses.

In convalescent patients relatively rapid remission of symptoms takes place. However, the patient who has had Japanese encephalitis remains physically and mentally weakened for a long time, and tires easily. In some patients mental disturbances of varying degree and neurological symptoms may persist for a long time, the latter being mainly related to diminished cortical activity. They may present different degrees of disturbance of co-ordination, motor apraxia, and so on.

Individuals who have had Japanese encephalitis undoubtedly require a long follow-up by a neurological institution. They should be regarded as invalids, and treated accordingly.

DIAGNOSIS

The diagnosis of Japanese encephalitis and similar encephalitides is not difficult if the disease occurs at the usual season in an endemic focus. As is known, the complement-fixation test becomes positive from the 3rd to the 7th day of the disease, the maximum titres being reached by the 30th to 40th days. We have used this test widely. We have also used the neutralization test, which provides a diagnostic titre from the 7th to 14th days. The titre gradually increases to the 60th-70th day, and persists for many years. The complement-fixation test may be used as a method of laboratory diagnosis in the acute and early convalescent stages of the disease, while the neutralization test may be used for retrospective diagnosis. This applies also to mosquito and tick-borne encephalitides. Recently a method of serological diagnosis using tissue cultures has been successfully elaborated.

TREATMENT

Treatment of both mosquito- and tick-borne encephalitis is more or less the same, especially in the acute stage. In the experience of many clinicians in the USSR, including our collaborators, in the first days of the acute stage injection of convalescent serum is to be recommended. Twenty millilitres of serum are injected daily for 3-4 days in the first 5-7 days of the disease. If it is not available hyperimmune horse serum is used—10-15 ml of this serum by intramuscular injection with the same frequency. Horse serum must be thoroughly purified from extraneous proteins to avoid serum sickness or allergic disease, which could complicate the course of the encephalitis. Subarachnoid injection of convalescent serum and certainly of hyperimmune horse serum is not indicated, especially in Japanese encephalitis. The injection of serum later than the 7th day is not justified, as by that time virus has disappeared from the blood stream.

We reject blood transfusion, which is especially harmful in Japanese encephalitis because the permeability of vessel walls is affected and therefore administration of fluids, particularly into the blood stream, will only result in increase of oedema and aggravation of the patient's condition and may even lead to a fatal outcome.

In the acute stage gamma-globulin is much to be recommended. The dose is 15-30 ml daily, in three doses.

We did lumbar puncture only in the first days of the disease for diagnosis, and have never used it as a method of treatment. On the other hand, we used all the anti-oedema drugs, neostigmine as well as a 40% solution of glucose with ascorbic acid. We tried neostigmine¹ as early as in 1945 in the acute stage of Japanese encephalitis, with the object of reducing cerebral oedema and decerebrate muscular rigidity. We based this treatment on our theory of the

¹ Neostigmine is a synthetic drug identical with the natural alkaloid eserine. In comparison with neostigmine, eserine produces more toxic effects and, in particular, affects the autonomic nervous system more severely, causing nausea, vomiting, and marked changes in blood pressure and pulse rate. In view of this we prefer neostigmine.
We recommend at signs aim to normalize the stigmine and eliminate residual importance to processes in since stigmine was used in these conditions, and a detailed analysis of its action, including an electro-encephalogram, had been made. According to our observations it was effective (after 15-25 injections) in decreasing muscle tone and especially paralysis and paresis (Graščenkov, 1951).

As is known, neostigmine has some effect against oedema. We were convinced of this while using it in traumatic lesions of the brain and spinal cord to reduce muscular rigidity.

In the acute period of mosquito-borne Japanese encephalitis, after an injection of neostigmine, there was improvement of consciousness for some hours, and decreased decerebrate rigidity and muscular hypertension. Unfortunately, this effect was temporary; after 3-4 hours it had worn off. However, even this temporary effect produced by neostigmine was justified, since it decreased the severity of the condition considerably and helped establish the effects of other forms of treatment.

Treatment in the residual stage is also of great importance so as to prevent complications and eliminate residual effects, and to contribute to a rapid recovery. Since in this period there are still physical and mental fatigue, muscular weakness, and other signs of disturbance of the central nervous system and of lowered metabolism, treatment must aim at reversing these conditions as much as possible. We recommend not more than four subcutaneous injections of 1-1.5 ml neostigmine in 1:100 solution at intervals of 2-3 days.

Investigations in our laboratory show that neostigmine normalizes the conduction of impulses from neuron to neuron by improving the biochemical processes in the synapses (Graščenkov, 1946).

We also recommend a course of treatment with vitamins of the B group together with C and E and, later, A₃, B₆, and B₁₂, and with such hormones as ACTH and cortisone, for the regulation of the metabolism of the nervous system and the whole organism.

We have used oxygen therapy widely in the form of subcutaneous injections of up to 1000 ml, given into the front of the thigh. The treatment of viral infections by oxygen under pressure can be recommended. Symptomatic treatment to improve cardiovascular and respiratory function is also of great importance.

We emphasize the necessity of a nourishing diet and improvement of the patient's appetite, for which we recommend 100 ml of port or 30% pure alcohol twice a day before meals in the convalescent period.

Blood transfusion is strongly contra-indicated for all convalescents. Even drip transfusion in small amounts inevitably results in death, as we found to our regret in Manchuria.

Finally, exceptional attention must be paid to nursing, which often proves decisive for the life of the patient. Prevention and control of bedsores, steps against pulmonary oedema and cardiac weakness, care of the bladder, rectum, eyes and oral cavity may all in the long run decide whether the patient will live or not. That is why it is necessary to establish special units for patients and provide them with well-trained nurses and attendants in adequate number so that they can carry on the numerous therapeutic procedures regularly and at the proper time. It may be said without exaggeration that the percentage of deaths is related not only to the pathogenicity of the infecting virus but also to the quality of the treatment.

It follows from what has been said that the early discharge of patients is strongly contra-indicated. Even with the most favourable course and with rapid regression of symptoms, death may occur in a patient apparently recovering well. Patients should therefore stay in hospitals not less than a month and a half, and should undoubtedly undergo a neurological follow-up.

Survivors should if possible be used as donors of convalescent serum. Blood should not be taken earlier than a month and a half after the onset of the disease, and then only if the condition of the patient is relatively satisfactory, the blood picture normal, and cardiac action good. Nor should the patient be asked to furnish more than 100 ml of blood. The presence of neurological residual signs is an absolute contra-indication to taking blood.

**PREVENTION**

Preventive measures are general and specific. General preventive measures are those numerous aimed at reducing or completely eliminating the possibility of attack by mosquitos. They include the drainage of marshes, the use of different chemicals such as DDT to eliminate mosquitos, the treatment (both mechanical and chemical) of goats, cows, and other domestic animals when they are especially attacked by mosquitos.
For individual prevention, we use extensively as a mechanical protection from mosquitos clothes and masks impregnated with repellent chemicals.

As a specific measure against Japanese encephalitis vaccination has been used in the USSR since 1939, mouse-brain emulsions treated by formalin being employed. Vaccination is carried out by three intramuscular injections (of 1 ml each) two months before the epidemic season in the endemic foci, newcomers in particular and people doing special work in the field being vaccinated. The interval between the first and the second injections is one month. A mild febrile reaction to the vaccination may occur in a small percentage of cases, as well as a mild allergic reaction; this can easily be controlled by antihistamines.

This combination of general and specific measures, together with control of the vectors, has undoubtedly achieved considerable success in reducing the incidence of both mosquito- and tick-borne encephalitis in endemic foci in the USSR.

**RÉSUMÉ**


En ce qui concerne les lésions anatomiques, l'encephalite japonaise est une capillarite hémorragique toxique généralisée, avec exsudation et prolifération du virus dans le tissu cérébral qui s'œdématisait.

Sur le plan clinique il faut, selon l'auteur, diviser l'évolution en quatre grandes phases: phase d'attaque, durant deux ou trois jours, caractérisée par une température très élevée et un tableau infectieux sans signes de localisation; phase aiguë (s'étendant du troisième au sixième jour) au cours de laquelle le virus pénètre de façon diffuse dans le parenchyme cérébral, entraînant des phénomènes neurologiques très graves (rigidité de décérébration); phase de lente déférencement (du septième au dixième jour) signalée par une amélioration de la situation, bien que de nouvelles localisations neurologiques puissent se développer; phase de convalescence, très longue (de quatre à sept semaines), ralentie par la présence de manifestations neurologiques (hémiparésies, troubles de la coordination, etc.) ou psychiatriques (psychose maniaco-dépressive, délire, etc.), parfois hachée de complications graves (pneumonie, pyélite, escarres de décubitus, crises hypoglycémiques, etc.).

En ce qui concerne le mécanisme des symptômes, l'auteur insiste sur la responsabilité de l'hypothalamus. Il existe de façon constante au cours de l'encephalite japonaise une atteinte du centre de régulation thermique.

Du point de vue thérapeutique, l'auteur insiste d'une part sur l'utilisation du sérum de convalescent administré dans les premiers jours de la maladie, d'autre part sur le danger des transfusions de sang aussi bien à la période d'état que lors de la convalescence.

La prophylaxie spécifique est représentée par l'administration intramusculaire (deux mois avant la période d'épidémie) de vaccin à base d'émulsion de cerveau de souris traitée par le formol; vaccin utilisé en URSS depuis 1939.

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